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# The Increasing Prevalence of Acalculous Cholecystitis in Outpatients

## *Results of a 7-Year Study*

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Acute acalculous cholecystitis (AAC) is a disease that causes high rates of morbidity such as those traditionally observed in the critically ill. Recently we noted an increase in the *de novo* presentation of outpatients with this disease. Our aim was to characterize this disease in outpatients, identify risk factors, and assess clinical outcome. Therefore a 7-year review of the Yale experience with AAC was undertaken. Forty-seven patients were identified. Seventy-seven per cent (36 of 47 patients) developed AAC at home without evidence of acute illness or trauma, while 23% (11 of 47 patients) developed the disease while hospitalized. Significant vascular disease was observed in 72% of outpatients. A 38% morbidity rate and 6% mortality rate were observed. We conclude that AAC occurs commonly in elderly male outpatients with vascular disease and that these patients incur significant morbidity in association with this condition. AAC should be suspected and prompt surgical management instituted when these patients present with an acute right upper quadrant inflammatory process.

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challenge to the surgeon and is of undeniable significance in the context of biliary disease as a whole.

The first case of acute acalculous cholecystitis was reported by Duncan in 1844 in a patient who developed the disease after femoral hernia repair.<sup>7</sup> Few cases were reported in the subsequent century, many of which were caused by congenital anomalies such as kinking or fibrosis of the cystic duct as well as other less common etiologies such as polyarteritis nodosa or infection.<sup>8,9</sup> The disease reportedly increased in prevalence in the second half of the 20th century and gained wide notoriety when Lindberg reported 12 Vietnam War casualties who developed acalculous cholecystitis.<sup>10</sup> This prompted a review by Glenn<sup>11</sup> that clearly documented the increased morbidity and mortality rates associated with this condition. Furthermore they established a number of predisposing conditions such as trauma, previous surgery, sepsis, the postpartum state obesity, and cardiovascular disease.

Although previous reports have consisted almost exclusively of critically ill ICU patients, we have observed the *de novo* presentation of acute acalculous cholecystitis in an increasing number of patients in the absence of acute illness or traumatic injury. These have occurred mainly in elderly male outpatients. Of particular significance was the obvious presence of concomitant atherosclerotic vascular disease.

The aim of the present investigation is threefold: first to examine the prevalence of AAC in nonhospitalized patients; second to identify associated risk factors that might predispose to development of the disease; and third to assess the clinical course and outcome of patients identified as suffering from acute acalculous cholecystitis.

**A**CUTE ACALCULOUS CHOLECYSTITIS is a well-characterized clinical condition comprising between 2% and 12% of all cases of acute cholecystitis.<sup>1,2</sup> It has been reported to occur most commonly in the setting of major trauma, burns, sepsis, in childhood and as a postoperative complication for surgery unrelated to the biliary tree. Most recently it has been documented as a complication of hyperalimentation,<sup>3</sup> the acquired immune deficiency syndrome,<sup>4</sup> and as a possible antibiotic hypersensitivity reaction.<sup>5</sup> In comparison to ordinary acute cholecystitis, the acalculous variety has a higher likelihood of gangrene and perforation as well as significantly higher morbidity and mortality rates. Reported mortality rates have varied from 6% to as high as 67%, whereas mortality from ordinary acute cholecystitis is approximately 3%.<sup>6</sup> This disease therefore poses a significant

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## Materials and Methods

The hospital and pathologic records of all patients with acute acalculous cholecystitis within the Yale-affiliated hospital system (Yale–New Haven Hospital, the West Haven Veterans Administration Medical Center, and Bridgeport Hospital) from January 1, 1981 to December 31, 1987 were reviewed. Patients were considered to have acute acalculous cholecystitis if all radiologic imaging studies failed to demonstrate stones or sludge, no stones were noted during operation by the surgeon, and post-operative pathologic examination confirmed the diagnosis of acute cholecystitis in the absence of biliary calculi. Patients with previous abdominal complaints suggestive of biliary colic or chronic cholecystitis were excluded.

## Results

### Patient Population

A total of 2346 patients with acute cholecystitis were treated at the three hospitals from January 1, 1981 to December 31, 1987. Forty-seven patients (2%) fulfilled the criteria for the diagnosis of acute acalculous cholecystitis. Patients ranged from 27 to 89 years of age (mean, 65.5 years). There were 36 men and 11 women for a 3.3:1 male-to-female ratio.

### Development of Disease

Thirty-six patients (77%) developed acute acalculous cholecystitis as outpatients (Fig. 1). Eleven patients (23%) developed their disease in the hospital, of which seven (15%) were in the intensive care unit and four (8%) were on the hospital wards. Of the 11 hospitalized patients, 6 developed the disease in the postoperative phase of surgery unrelated to the biliary tree, 3 patients suffered traumatic injuries, 1 patient suffered an acute myocardial infarction, and 1 woman developed the disease 3 weeks postpartum.

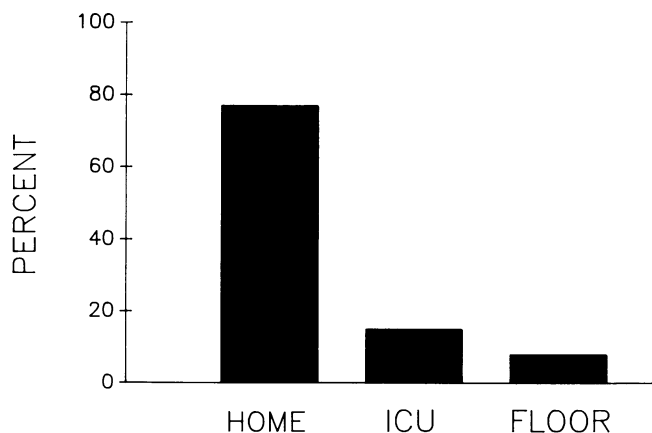


FIG. 1. Development of disease in 47 patients with acute acalculous cholecystitis.

TABLE 1. *Presenting Signs and Symptoms in 47 Patients with Acute Acalculous Cholecystitis*

Symptoms/Signs	Percentage
Abdominal Pain	
Right upper quadrant	83
Epigastric	9
Diffuse	9
Fever	55
Leukocytosis	96
Jaundice	4
Nausea and vomiting	6
Septic shock	4

### Presenting Signs and Symptoms

Right upper quadrant pain was the most common symptom in both groups and occurred in 83% of the patients (Table 1). This was accompanied by fever in 55%. Less common presentations included diffuse abdominal pain, epigastric pain, and nausea and vomiting. Uncommon presentations observed only in outpatients included septic shock (4%) and jaundice (4%).

### Diagnostic Modalities

Thirty-six patients underwent hepatiminodiacetic acid (HIDA) scanning, of which 35 (97%) were positive (Table 2). Of the 18 patients who underwent abdominal ultrasound, only 5 (28%) had evidence of acute cholecystitis and three of the four patients who underwent CT scan had evidence of cholecystitis. Five patients who were operated on for peritonitis had the diagnosis made solely on operative findings. In these patients preoperative diagnoses included acute appendicitis (2), ruptured abdominal aortic aneurysm (1), and sepsis of unknown etiology (2). The average diagnostic delay observed (defined as the time elapsed between the stated onset of symptoms and time of diagnosis) was  $36.9 \pm 5.1$  hours. Twenty-one patients (45%) were admitted with a diagnosis other than cholecystitis.

### Coexisting Morbidity

Thirty-nine patients (82%) were known to have underlying major medical problems (Table 3). Of those who developed their disease at home, 72% had atherosclerotic vascular disease, including hypertension (57%), symp-

TABLE 2. *Accuracy of Diagnostic Modalities Used in 47 Patients with Acute Acalculous Cholecystitis*

Examination	No. of Patients	% Accuracy
HIDA scan	36	97
Ultrasound	18	28
CT scan	3	75
Laparotomy	5	100

TABLE 3. *Atherosclerotic Vascular Disease in 36 Outpatients with Acute Acalculous Cholecystitis*

Medical Problem	No. of Patients	Percentage
Hypertension	20	56
Angina/myocardial infarction	11	31
Congestive heart failure	2	6
Peripheral vascular disease	3	8
Cerebrovascular disease	3	8
Diabetes	6	15

tomatic coronary artery disease or previous myocardial infarction (31%), cerebral or peripheral vascular disease (8%), and diabetes (15%). Alcoholic liver disease and chronic obstructive pulmonary disease were observed in 15%, and 4% had peptic ulcer disease.

### Treatment

Cholecystectomy was performed in 42 patients (89%), while cholecystostomy was performed in five patients (11%). All cholecystectomy specimens had gross and microscopic evidence of acute cholecystitis with no stones present. Gangrene was noted in 13 (28%) operative specimens.

### Morbidity and Mortality

Eighteen patients (38%) developed a total of 24 complications (Table 4). The incidence was slightly higher in outpatients (41%). Major complications were most commonly cardiopulmonary or septic in nature. Three patients died, two due to myocardial infarction and the other due to sepsis. All three were critically ill inpatients.

### Discussion

In this study we have documented that the majority of patients who developed acute acalculous cholecystitis over a 7-year period were outpatients rather than critically ill inpatients, as previously reported. Seventy-two per cent had significant atherosclerotic vascular disease, including symptomatic coronary artery disease, cerebral or peripheral atherosclerosis, and diabetes mellitus. Alcoholic liver disease and chronic obstructive pulmonary disease were also commonly observed. As might be predicted, the most common presentation was that of right upper quadrant pain, fever, and leukocytosis. HIDA scan was the most reliable diagnostic modality. All patients were treated surgically and a 38% morbidity rate and 6% mortality rate were observed.

The age at onset and sex distribution of patients with acalculous cholecystitis is markedly different than those of patients with ordinary acute cholecystitis. While calculous gallbladder disease is most common in the fourth and fifth decades; 242 patients with acalculous cholecys-

titis from the literature had an average age of 64.3 years.<sup>2,10,12</sup> In this respect the Yale series correlates with other series with an average age of 65.5 years.

Although calculous gallbladder disease is much more common in women than in men, most major series of patients with acalculous cholecystitis have revealed a male predominance. Glenn<sup>11</sup> noted a male-to-female ratio of 1.5:1, Johnson<sup>2</sup> noted a 2.6:1 ratio among his patients, and although Fox<sup>1</sup> noted an equal prevalence in both sexes, no study as yet has noted a female predominance. The present series concurs with these findings with a 3.3:1 male-to-female ratio. However this ratio may be skewed because approximately 30% of patients in this study were from the Veteran's Administration Medical Center, an almost exclusively male population. Among patients from the two other hospitals in this study, a male-to-female ratio of 2.8:1 was observed.

In no series published to date have a significant number of relatively healthy outpatients developed acute acalculous cholecystitis. However 77% of patients with this disease reported here presented *de novo* without any of the generally accepted prodromal conditions. Eighty-three per cent of our patients had significant underlying medical problems and 72% had evidence of underlying vascular disease. Although several large series have observed that acute acalculous cholecystitis occurs in medically compromised patients, this series reports the highest percentage observed thus far.<sup>2</sup> Cardiovascular disease in particular was noted by Glenn<sup>11</sup> in 50% of the patients in his original series.

Recently several authors have postulated a role for gallbladder ischemia in the pathogenesis of this disease. This may be secondary to shock from hypovolemia and/or sepsis. Visceral vasoconstriction due to increased sym-

TABLE 4. *Complications in 47 Patients with Acute Acalculous Cholecystitis*

Complication	Number
Major complications	
Myocardial infarction	2
Sepsis	4
Pneumonia/ARDS	4
Arrhythmias	2
Heart failure	1
Deep vein thrombosis	1
Dehiscence	1
Pancreatitis	1
Intra-abdominal abscess	1
Total	17
Minor complications	
Urinary tract infection	3
Wound infection	2
Ileus	1
Mental status changes	1
Total	7

pathetic tone characteristic of the postoperative state or from administration of inotropic drugs may further exacerbate this ischemia. By analogy with stress gastritis and mesenteric ischemia, the resultant reduction in gallbladder blood flow may render the mucosa more susceptible to the noxious effects of bile and thereby further predispose to the development of cholecystitis. This theory is supported by experimental evidence as well. Using an *in vivo* canine model, Dillon et al.<sup>13</sup> demonstrated that inhalation of the constituents of cigarette smoke condensate (tar) resulted in the prompt development of acute acalculous cholecystitis and pneumonitis with thrombus formation in pulmonary vessels.

Virtually every series of patients with acalculous cholecystitis has documented that the majority of patients present with right upper quadrant pain, fever, and leukocytosis. However these findings may be masked in postoperative or post-traumatic patients who are intubated, neurologically impaired, or heavily sedated. The diagnosis may thus be difficult and contribute to the diagnostic and therapeutic delay. In the series reported here, 83% suffered right upper quadrant pain, 55% had fever, and all had leukocytosis greater than 10,000/mm<sup>3</sup>. Despite this 45% of patients were admitted with a diagnosis other than acute cholecystitis. There was no significant difference between inpatients and outpatients with respect to presentation.

The diagnostic delay associated with identification of patients with acalculous cholecystitis may be significant and has been implicated in the increased incidence of gangrene, empyema, and perforation that has been observed. Johnson<sup>2</sup> found that 40% of patients who underwent operation more than 48 hours after the onset of symptoms suffered gallbladder perforation. Conversely only 8% of patients managed without delay in surgical treatment had perforations. However other studies have not corroborated this finding. Fox noted twice the incidence of gallbladder gangrene in patients who were operated on immediately after resuscitation,<sup>1</sup> while Long, observed no higher incidence of gangrene despite an average diagnostic delay of 3 weeks in patients with post-traumatic acalculous cholecystitis.<sup>14</sup> From these studies it appears probable that diagnostic delay is not the only factor responsible for the development of gallbladder gangrene in these patients. The average diagnostic delay in the series reported here was  $36.9 \pm 5.1$  hours and 28% were noted to have gangrenous gallbladders.

The diagnostic modality of choice in patients with ordinary acute cholecystitis is hepatobiliary scanning, a test that is both highly sensitive (95% to 100%) and specific (81% to 100%).<sup>15,16</sup> It has also been used with success in patients with acalculous cholecystitis, in which reported sensitivities range from 68% to 100%.<sup>17-19</sup> However, if false positive results are included, the actual sensitivities

may be as low as 38%. A factor contributing to this may be the observation that approximately one third of patients without clinical evidence of acute cholecystitis who are fasting and receiving total parenteral nutrition will have false-positive hepatobiliary scans.<sup>20</sup> In these patients ultrasonography may be useful if the gallbladder wall is thickened ( $\geq 4$ mm) and subserosal edema or pericholecystic fluid is present.<sup>21</sup> Computed tomographic scanning may also be a useful diagnostic aid, and recently <sup>111</sup>Indium-labeled leukocytes have also been used with some success.<sup>22</sup> In the Yale series, 97% of patients had positive scans and false positives were not recorded. Ultrasound was positive in 48% of the 18 patients in whom it was used and in three of four patients CT scan was required for the diagnosis. From the above it seems clear that hepatobiliary scanning is the diagnostic test of choice but in special circumstances ultrasonography and CT scanning may be useful diagnostic adjuncts.

Morbidity and mortality rate in patients with ordinary acute cholecystitis are remarkably low. Glenn reported a 1.7% mortality rate in more than 4000 cholecystectomies performed between 1932 and 1977.<sup>23</sup> In contrast morbidity and mortality rates for patients with acute acalculous cholecystitis are substantially higher. Reported mortality rates vary from 6.5% to 67%, with morbidity approaching 100% in some series.<sup>1,6,14</sup> This has been attributed by various authors to disease virulence, host compromise, diagnostic delay, and to a combination of such factors. The overall morbidity rate observed in this series (38%) is similar to that found by others, and the mortality rate of 6% compares quite favorably to other studies of comparable size. Although morbidity and mortality of this magnitude has come to be expected in patients with acute acalculous cholecystitis, the morbidity rate observed for outpatients in this series (41%) is significantly higher than would be expected for patients with ordinary acute cholecystitis. None of the patients in the outpatient group died as a result of their disease.

The most striking finding of this review is that acute acalculous cholecystitis occurs with relatively high frequency in healthy male patients who are older and have a high incidence of atherosclerotic vascular disease. These patients incurred significantly higher morbidity than would be expected despite prompt diagnosis and surgical intervention. These observations must be juxtaposed with previous studies that, while noting a male predominance and older average age, have characterized acalculous cholecystitis as one observed exclusively in critically ill patients. This report provides evidence for expanding the high-risk category to include elderly male patients with concomitant atherosclerotic vascular disease and mandates aggressive surgical management of these patients when evidence of a right upper quadrant inflammatory process is present.

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